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Europäisches
Patentamt

Zweigstelle
in Den Haag
Recherchen-
abteilung

European
Patent Office

Branch at
The Hague
Search
division

Office européen
des brevets

Département à
La Haye
Division de la
recherche

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18. Jan. 2001

Frist
bearb.:

Datum/Date

15. 01. 01

Zeichen/Ref./Réf.

D 2822 EP

Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°.

98931354.9

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire

Diversa Corporation

COMMUNICATION

The European Patent Office herewith transmits

- ☐ the European search report
- ☐ the declaration under Rule 45 EPC
- ☐ the partial European search report under Rule 45 EPC
- ☒ the supplementary European search report concerning the international application under Article 157(2) EPC relating to the above-mentioned European patent application. Copies of the documents cited in the search report are enclosed.

The following specifications given by the applicant have been approved by the Search Division :

☒ Abstract

☒ Title

☐ Figure

☐ The abstract was modified by the Search Division and the definitive text is attached to this communication.

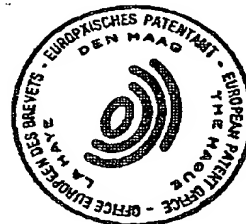
☐ The following figure will be published with the abstract, since the Search Division considers that it better characterises the invention than the one indicated by the applicant.

Figure:

☒ Additional copy(copies) of the documents cited in the European search report.

REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.



M. Claudepierre



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.CI.6)
E	WO 98 41869 A (CHROMAXOME CORP) 24 September 1998 (1998-09-24) * page 15, line 4 - line 15 * * page 23, line 22; claims 1-32; example 5.1 * ---	1-12, 18-20, 62-64	C12N15/10 C12Q1/68
E	WO 99 10539 A (DIVERSA CORP) 4 March 1999 (1999-03-04) * page 6, line 25 - page 10, line 29 * * page 37, line 9 - page 40, line 6 * ---	1-64	
Y	WO 96 34112 A (CHROMAXOME CORP) 31 October 1996 (1996-10-31) * page 68, line 1 - page 71, line 37 * * page 84, line 30 - page 86, line 8; claims 1-41; figure 8 * * page 88, line 6 - page 89, line 12 * * page 102, line 25; examples 6.2-6.6 * * page 101, line 1 - line 14 * * page 90, line 33 - page 91, line 22 * ---	1-20, 28-64	
Y	WO 97 20918 A (RECOMBINANT BIOCATALYSIS INC) 12 June 1997 (1997-06-12) * claims 1-26 * ---	28-46	TECHNICAL FIELDS SEARCHED (Int.CI.6) C12N C12Q
Y	WO 95 26400 A (ONYX PHARMA INC) 5 October 1995 (1995-10-05) * claims 1-17 * ---	47-61	
Y	WO 97 04077 A (MARRS BARRY ;SHORT JAY M (US); STEIN JEFFREY L (US); RECOMBINANT B) 6 February 1997 (1997-02-06) * page 11, line 13 - page 12, line 4; claim 8 * --- -/--	62-64	
The supplementary search report has been based on the last set of claims valid and available at the start of the search.			
Place of search THE HAGUE		Date of completion of the search 9 January 2001	Examiner Hornig, H
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.CI.6)
Y	WO 97 20078 A (AFFYMAX TECH NV ; CRAMER ANDREAS (US); STEMMER WILLEM P C (US)) 5 June 1997 (1997-06-05) * the whole document *	62, 64	
D, A	WITTRUP K D ET AL: "Microencapsulation selection for isolation of yeast mutants with increased secretion of Aspergillus awamori glucoamylase." BIOTECHNOLOGY AND BIOENGINEERING, vol. 42, no. 3, 1993, pages 351-356, XP002151519 ISSN: 0006-3592 * the whole document *		
A	WO 94 10300 A (GEN HOSPITAL CORP) 11 May 1994 (1994-05-11) * page 40, line 23 - page 43, line 19 *		
A	ROESSNER CHARLES A ET AL: "Fluorescence-based method for selection of recombinant plasmids." BIOTECHNIQUES, vol. 19, no. 5, 1995, pages 760, 762-764, XP002151562 ISSN: 0736-6205 * the whole document *		TECHNICAL FIELDS SEARCHED (Int.CI.6)
A	US 4 801 529 A (PERLMAN DANIEL) 31 January 1989 (1989-01-31) * the whole document *		
P, A	WO 97 48717 A (RECOMBINANT BIOCATALYSIS INC) 24 December 1997 (1997-12-24) * the whole document *		
The supplementary search report has been based on the last set of claims valid and available at the start of the search.			
Place of search THE HAGUE		Date of completion of the search 9 January 2001	Examiner Hornig, H
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			



CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:



The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-20, 62-64

A method for identifying bioactivities or biomolecules using high throughput screening of genomic DNA samples to identify one or more enzymes encoded by the DNA of said sample, comprising: a) providing an expression library containing a plurality of clones, wherein the DNA for generating the library is obtained from a mixed population of organism; b) inserting bioactive fluorescent substrate in at least one clone of the library wherein the substrate is fluorescent in the presence of a bioactivity or biomolecule; c) screening the clones with a fluorescent analyzer that detects bioactive fluorescence; and d) identifying clones detected as positive for bioactive fluorescence, wherein fluorescence is indicative of DNA that encodes an bioactivity or biomolecule; said method, wherein the sample is encapsulated in a gel microdrop; said method, wherein the expression library contains DNA from extremophiles; said method, wherein the bioactive substrate comprises C12FDG; said method including the additional steps of: subjecting an enzyme encoded by the DNA identified in step d) to directed evolution comprising the step of: a) subjecting the enzyme to non-directed mutagenesis; and b) screening mutant enzymes produced in step a) for a mutant enzyme; said method for identifying bioactivities or biomolecules using high throughput screening of genomic DNA in a culture-independent system; said method further comprising encapsulation the clones and the bioactive substrate prior to screening; said method wherein the expression library is procaryotic.

2. Claims: 21-27

A method of screening for an agent that modulates the activity of a target cell component, wherein the target cell component and a selectable marker are expressed by a recombinant cell, the method comprising co-encapsulating the agent in a micro-environment with the recombinant cell expressing the target cell component and detectable marker and detecting the effect of the agent on the activity of the cell component; said method wherein the agent is a transducing protein, said protein is a G-protein;

3. Claims: 28-46

A method for enriching for target DNA sequences containing at least a partial coding region for at least one specified activity in a DNA sample comprising: a) co-encapsulating in a micro-environment a mixture of target DNA obtained from a mixture of organisms with a mixture of target DNA probes



The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

comprising a detectable marker and at least a portion of a DNA sequence encoding at least one enzyme having a specified enzyme activity; b) incubating the co-encapsulated mixture under such conditions and for such time as to allow hybridization of complementary sequences; and c) screening for the specified activity;

4. Claims: 47-61

A method of screening for an agent that modulates the interaction of a first test protein linked to a DNA binding moiety and a second test protein linked to a transcriptional activation moiety, comprising co-encapsulating the agent with the first test protein and second test protein in a suitable microenvironment and determining the ability of the agent to modulate the interaction of the first test protein linked to a DNA binding moiety with the second test protein covalently linked to a transcriptional activation moiety, wherein the agent enhances or inhibits the expression of a detectable protein, and wherein the enhancement or inhibition is detected by FACS analysis;

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 98 93 1354

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

09-01-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9841869 A	24-09-1998	AU 6571598 A	12-10-1998
		EP 0975969 A	02-02-2000
WO 9910539 A	04-03-1999	US 6057103 A	02-05-2000
		AU 8923198 A	16-03-1999
		EP 1025262 A	09-08-2000
WO 9634112 A	31-10-1996	AU 723619 B	31-08-2000
		AU 5804996 A	18-11-1996
		CA 2219136 A	31-10-1996
		EP 0822990 A	11-02-1998
		HU 9801871 A	30-11-1998
		JP 11504218 T	20-04-1999
		US 5824485 A	20-10-1998
WO 9720918 A	12-06-1997	US 5939250 A	17-08-1999
		US 6054267 A	25-04-2000
		AU 720334 B	25-05-2000
		AU 1148997 A	27-06-1997
		CA 2239686 A	12-06-1997
		EP 0866853 A	30-09-1998
		JP 2000501606 T	15-02-2000
		US 5962283 A	05-10-1999
		US 6030779 A	29-02-2000
WO 9526400 A	05-10-1995	US 5525490 A	11-06-1996
		AU 2779095 A	17-10-1995
WO 9704077 A	06-02-1997	US 6004788 A	21-12-1999
		US 5958672 A	28-09-1999
		AU 6547796 A	18-02-1997
		EP 0839185 A	06-05-1998
		US 6057103 A	02-05-2000
		US 6030779 A	29-02-2000
WO 9720078 A	05-06-1997	US 5811238 A	22-09-1998
		US 6117679 A	12-09-2000
		AU 713952 B	16-12-1999
		AU 1087397 A	19-06-1997
		CA 2239099 A	05-06-1997
		EP 0876509 A	11-11-1998
		EP 0911396 A	28-04-1999
		JP 2000500981 T	02-02-2000
		AU 2542697 A	17-10-1997
		CA 2247930 A	02-10-1997
		EP 0906418 A	07-04-1999

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 98 93 1354

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

09-01-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9720078 A		JP 2000507444 T WO 9735966 A US 5837458 A	20-06-2000 02-10-1997 17-11-1998
WO 9410300 A	11-05-1994	EP 0672131 A JP 8506480 T US 5580736 A US 5786169 A	20-09-1995 16-07-1996 03-12-1996 28-07-1998
US 4801529 A	31-01-1989	NONE	
WO 9748717 A	24-12-1997	US 5763239 A AU 718573 B AU 3406697 A CA 2258175 A EP 0923598 A JP 2000513933 T US 6001574 A	09-06-1998 13-04-2000 07-01-1998 24-12-1997 23-06-1999 24-10-2000 14-12-1999

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: LISA A. HAILE	
FISH & RICHARDSON P.C.	
4225 EXECUTIVE SQUARE, SUITE 1400	
LA JOLLA, CALIFORNIA 92037	
Docketed By Practice Systems	
PCT Search Report	
Deadline: 11-24-98	
Foreign art (09010/020001)	
Deadline: 12-24-98	
Initials:	Brrr
Record:	P 28972USD

PCT

SEP 29 1998

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

Docketed By	Billing Secretary
Due Date:	
Deadline:	(PCT Rule 44.1)
Initials:	

Date of Mailing
(day/month/year)

24 SEP 1998

Applicant's or agent's file reference 09010/039WQI 09010/035W01	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US98/12674	International filing date (day/month/year) 16 JUNE 1998
Applicant DIVERSA CORPORATION	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer JAMES KETTER <i>JAB for</i>
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 09010/039WO1	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US98/12674	International filing date (<i>day/month/year</i>) 16 JUNE 1998	(Earliest) Priority Date 16 JUNE 1997
Applicant DIVERSA CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (See Box I).

2. ☐ Unity of invention is lacking (See Box II).

3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.
☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ transcribed by this Authority.

4. With regard to the title,

☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:
 Figure No. _____

☐ as suggested by the applicant.
☐ because the applicant failed to suggest a figure.
☐ because this figure better characterizes the invention.

☒ None of the figures.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: LISA A. HAILE
FISH & RICHARDSON P.C.
4225 EXECUTIVE SQUARE, SUITE 1400
LA JOLLA, CALIFORNIA 92037

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 09010/039WO1	Date of Mailing (day/month/year) FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US98/12674	International filing date (day/month/year) 16 JUNE 1998
Applicant DIVERSA CORPORATION	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.
Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.
2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
4. **Further action(s):** The applicant is reminded of the following:
 Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.
 Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).
 Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JAMES KETTER Telephone No. (703) 308-0196
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INTERNATIONAL SEARCH REPORT

international application No.

PCT/US98/12674

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C12Q 1/68

US CL : 435/6

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, MEDLINE**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 5,663,046 A (BALDWIN et al.) 02 September 1997, see entire document.	1-77
A	PLOVINS, A. et al. Use of Fluorescein-Di-β-D-Galactopyranoside (FDG) and C ₁₂ -FDG as Substrates for β-Galactosidase Detection by Flow Cytometry in Animal, Bacterial, and Yeast Cells. Applied and Environmental Microbiology. December 1994, Vol. 60, No. 12, pages 4638-4641, see entire document.	1-77



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

24 AUGUST 1998

Date of mailing of the international search report

24 SEP 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JAMES KETTER

Telephone No. (703) 308-0196